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Attorney Docket No. 27412U

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PALMER

Attorney: GMN/SMM

Serial No.: 10/582,395

Filed: June 12, 2006

International Appl. No.: PCT/EP2004/053560

International Filing Date: 17 December 2004 (17.12.2004)

Title: **TRICYCLIC IMIDZOPYRIDINES FOR USE AS GASTRIC SECRETION INHIBITORS**

TRANSMITTAL LETTER


Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450  
Sir:

Submitted herewith for filing in the U.S. Patent and Trademark Office is the following:

- (1) Transmittal Letter;
- (2) Submission of the International Preliminary Report of Patentability;
- (3) Copy of Form/IB 373 (International Preliminary Report on Patentability);
- (4) Copy of Form PCT/ISA/237 (Written Opinion of the International Searching Authority).

The Commissioner is hereby authorized to charge any deficiency or credit any excess to Deposit Account No. 14-0112.

Respectfully submitted,  
**NATH & ASSOCIATES PLLC**

By:   
Gary M. Nath  
Registration No. 26,965  
Sheldon M. McGee  
Registration No. 50,454  
Customer No. 34375

Date: July 11, 2006  
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**SUBMISSION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:


To supplement the documents filed with the National Phase Filing Under 35 USC 371 of the above captioned application commenced on 12 June 2006, applicant hereby submits the PCT International Preliminary Report on Patentability (PCT/IB/373), and Written Opinion of the International Searching Authority (Form PCT/IPEA/409).

If the Examiner has any questions or wishes to discuss this application, kindly telephone the undersigned at the below-listed number.

Respectfully submitted,

**NATH & ASSOCIATES PLLC**

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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 1224WOORD01	<b>FOR FURTHER ACTION</b>	See item 4 below
International application No. PCT/EP2004/053560	International filing date ( <i>day/month/year</i> ) 17 December 2004 (17.12.2004)	Priority date ( <i>day/month/year</i> ) 19 December 2003 (19.12.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant ALTANA PHARMA AG		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input type="checkbox"/>            | Box No. II   | Priority  |
| <input checked="" type="checkbox"/> | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/>            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input type="checkbox"/>            | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

Date of issuance of this report  
20 June 2006 (20.06.2006)

Authorized officer:

**Agnes Wittmann-Regis**

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Form PCT/IB/373 (January 2004)

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

REC'D 23 FEB 2005

WIPO

PCT

PCT

To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing

(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

### FOR FURTHER ACTION

See paragraph 2 below

International application No.  
PCT/EP2004/053560

International filing date (day/month/year)  
17.12.2004

Priority date (day/month/year)  
19.12.2003

International Patent Classification (IPC) or both national classification and IPC  
A61K31/454, A61P1/04, C07D491/14

Applicant  
ALTANA PHARMA AG

### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
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Authorized Officer

Johnson, C

Telephone No. +49 89 2399-8287



**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/053560

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/053560

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 16

because:

☒ the said international application, or the said claims Nos. 16 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/EP2004/053560

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**Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-16
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-16
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

**III. Non-establishment of opinion**

Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**V. Reasoned statement**

Reference is made to the following documents:

D1: WO 03/014123

D2: WO 02/34749

**Novelty**

Although D1 mentions that the pure enantiomers of the compounds of formula 1 are the preferred subject matter of the invention (p. 6, 4th full paragraph), the (S)-enantiomer of the present invention is not directly and unambiguously disclosed in this document, and present claim 1 may be considered to be a novel selection from the disclosure of D1. The compounds of D2 differ from claim 1 because the pyran ring is substituted at the 4-position (i.e. one of R4a and R4b  $\neq$  H).

Claims 1-16 fulfil the requirements of Article 33(2) PCT.

**Inventive step**

The technical problem underlying the present invention appears to be the provision of improved gastric acid secretion inhibitors. D1 may be considered the closest prior art. It has been shown that selected compounds of present claim 1 have an improved activity compared with their corresponding (R)-enantiomers (p. 79).

The question that must be answered is whether it is non-obvious that one enantiomer of a chiral compound has improved activity compared with the other or with the racemate. In decision T296/87 (OJ 1990, 195) the Technical Board of Appeal



discussed this question. Their conclusion was as follows (point 8.4.1): *"Long before the contested patent's priority date, it was generally known to specialists that, in physiologically active substances (e.g. herbicides, fungicides, insecticides and growth regulators, but also pharmaceuticals and foodstuffs) with an asymmetrical carbon atom enabling them to occur in the form of a racemate or one of two enantiomers, one of the latter frequently has a quantitatively greater effect than the other or than the racemate. If - as here - the aim is therefore to develop agents with increased physiological activity from a physiologically active racemate the obvious first step - before any thought is given, say, to synthesising structurally modified products - is to produce the two enantiomers in isolation and test whether one or the other is more active than the racemate. Such tests are routine. Under established Board case law, an enhanced effect cannot be adduced as evidence of an inventive step if it emerges from obvious tests."*

In point 8.4.2 cases are given where the above generalisation cannot be applied. However, these cases do not appear to apply to the present application. Indeed, D2 (formula 1\*, p. 38) shows that at the priority date of the present application it was known, not only in general, but also for structurally very similar compounds with the same biological activity, that one of the enantiomers, specifically the (S)-enantiomer, was preferred.

It would thus be obvious for the skilled person, with the common general knowledge that one enantiomer is often more active than the other or than the racemate (and with D2 showing that this generalisation is indeed applicable to gastric acid secretion inhibitors with the present tricyclic fused core), to solve the technical problem by providing the separate enantiomers and by testing them to ascertain which enantiomer has the higher activity.

Claims 1-16 therefore do not fulfil the requirements of Article 33(3) PCT.

#### **Industrial applicability**

Claims 1-15 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present